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Squamous Cell Carcinoma of the Oral Tissues: A Comprehensive Review for Oral Healthcare Providers

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Abstract

North Americans in 2004 were projected to die from oral and pharyngeal cancer at a rate of 1.2 per hour. Oral healthcare providers can be instrumental in reducing the incidence of oral and pharyngeal premalignant and malignant lesions by identifying patients with high-risk behavior, educating their patients about the consequences of their high-risk behavior, and by early detection of premalignant and malignant conditions. The fact only 34% of the cancers of the oral cavity and larynx are localized at the time of diagnosis and evidence that at least one third of the patients diagnosed with an oral or pharyngeal malignancy have undergone oral cancer screening within the past three years suggests the current protocol for the early detection of pre-malignant or malignant changes appears to be deficient. To facilitate early diagnosis, oral healthcare providers must take into consideration the capriciousness of oral cancer and must be familiar with the availability and application of diagnostic modalities beyond conventional visual inspection and palpation of oral soft tissues. This article provides a comprehensive review of the disease for healthcare professionals.

Keywords: Oral cancer, oral healthcare providers, high risk oral lesions, early diagnosis, management

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Etiology and Epidemiology

Cancer may be defined as uncontrolled tissue growth in susceptible patients, which results from an imbalance between cell division and programmed cell death (apoptosis).[1] Among the known factors implicated as potential "initiators" and/or "promoters" of cancer are: tobacco, alcohol, solar radiation, ionizing radiation, occupational carcinogens, environmental pollutants, medications, infectious agents, and nutrients. Regardless of the accelerating factors, neoplasms arise clonally from transformed cells that have undergone specific genetic and epigenetic alterations in oncogenes or tumor-suppressor genes.[1] Oncogenes are normal genes that are involved in physiological processes and whose excessive function (through amplification or mutation) is associated with cancer. An epigenetic alteration implicated in cancer biology is methylation; a form of gene silencing that may involve tumor-suppressor genes. These are also normal genes that have important functions in cell homeostasis and whose absent function (through methylation, deletion, or mutation) is associated with the neoplastic phenotype. A third set of cancer-related genes is represented by genes that encode DNA-repairing enzymes and whose alterations are also associated with malignancy.[2] These genetic and epigenetic mechanisms affect the expression of cell cycle regulatory proteins, such as cyclin-dependent kinases, which govern the initiation, progression, and completion of cell cycle events, causing overexpression of cyclins and loss of expression of cyclin-dependent kinase inhibitors.[3] A major consequence is deregulated cyclin-dependent kinase activity, which provides malignant cells with a selective growth advantage.

Over 90% of oral and pharyngeal cancers are squamous cell carcinomas (SCCs). Tobacco is the major risk factor associated with oral SCC among current and recent ex-smokers in comparison to non-smokers and ex-smokers (>20 years).[4-7] Self-reported data from the 2002 National Health Interview Survey indicated, in 2002, approximately 22.5% (45.8 million) of adults were current smokers; of these, an estimated 37.5 million smoked every day and 8.3 million smoked some days.[8] In addition an estimated 46.0 million adults reported to be former smokers, representing 50.2% of adults who had ever smoked. The prevalence of smoking was higher among men (25.2%) than women (20.0%) and inversely related to age, from 28.5% for those aged 18-24 years to 9.3 for those aged > 65 years. Current smoking prevalence was higher among adults living below the poverty level (32.9%) than among those at or above the poverty level (22.2%). Smoking prevalence was highest among adults who had earned a General Educational Development diploma (43.30%) and lowest among those with graduate degrees (6.4%). Additionally, a dose-risk relationship between tobacco and/or alcohol (with tobacco a much stronger independent risk factor) and the development of oral cancer has been noted.[9] Other studies implicate human papilloma viruses (most frequently HPV-16 and HPV-18) in the pathogenesis of oral SCCs.[10-15] Additional risk factors such as living in rural areas, socioeconomic status, age, gender, mouthwashes, and humoral and cellular immune mechanisms play less well understood roles.[16-22] Chronic periodontal disease, poor oral hygiene, ill-fitting dentures, sharp teeth, electrogalvanism, and edentulism have been suggested as cofactors.[23-25]

Oral cancer consistently ranks as one of the top ten cancers worldwide, with broad differences in geographic distribution.[26] In the United States the number of new cancer cases for 2004 reached 1,368,030.[27] Of these newly diagnosed cases, approximately 28,260 were malignancies of the oral cavity and pharynx. While this represents < 3% of all malignant neoplasms diagnosed annually in the United States[27], in developing countries the incidence is much higher.[6, 20] Despite the relatively

constant prevalence of oral cancer in the United States, national trends in the past 50 years have shown some significant epidemiological changes. Oral cancer remains predominantly a disease of males. However, the male to female ratio has steadily shifted from 6:1 in 1950 to 2:1 in 1997.[28] The changing ratio is likely the result of the increase in smoking among women in the past three decades. In addition cancer is an age-related disease, and in the United States the number of women aged >65 years now exceeds the number of men aged >65 years by almost 50%. Also, while the number of affected white males in the United States has steadily decreased from 1973 to 1996, during the same time period, a disturbing increase of this disease among African-American males has been noted.[29] Most cases of oral cancer in the United States are diagnosed in the sixth and seventh decades of a person's life, with the highest prevalence noted in patients over 65. However, a recent study in the United States reported an alarming increase in the incidence of oral cancer, particularly tongue cancer, in young white males under the age of 40.[29]

Clinical Presentation

Squamous Cell Carcinoma (SCC)

Over 90% of head and neck cancers are SCC.[30, 31] Overt SSC typically presents as a persistent mass, nodule, or indurated ulcer (Figure 1). Color changes are common and consist of red or red and white hues. Involvement of adjacent tissues is possible, though not necessary, and represents local invasion of the tumor. Symptoms are uncommon in earlier stages of the disease but become frequent with advanced local invasion. In particular paresthesia and anesthesia in the absence of a history of trauma are highly suggestive of an invasive malignancy. Metastatic dissemination occurs through the submandibular, cervical (Figure 2), and jugular lymphatic pathways and distant metastases most commonly spread to the lungs. The majority of intraoral SCCs originate from non-keratinized mucosa. The three most common sites of involvement are the tongue (30%), lip (17%), and floor of the mouth (14%).[29] Recently, a trend toward increased numbers of lesions arising on both the dentate and edentulous gingiva was reported (Figure 3).[32]

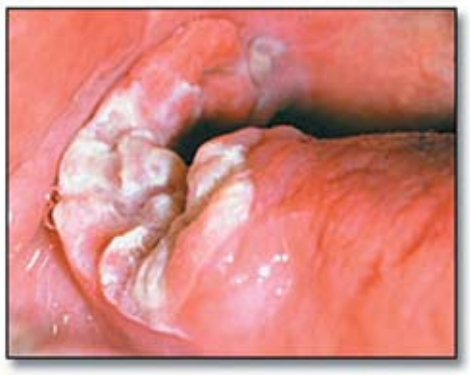


Figure 1. Overt SCC typically presents as a persistent mass, nodule, or indurated ulcer.

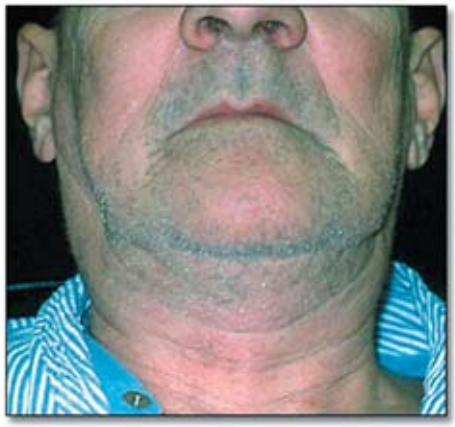


Figure 2. Metastatic dissemination of SCC into the right cervical lymphatic pathway.

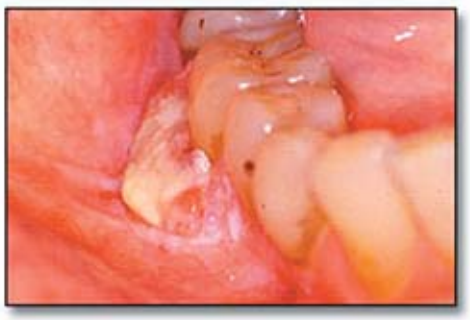


Figure 3. Recently, an increased incidence of SCC on the gingiva was reported.

High Risk Lesions

Erythroplakia

Erythroplakia is a descriptive clinical term for any red macular lesion affecting the oral mucosa, which cannot be given a specific clinical diagnosis.[33] Erythroplakia may manifest as a homogenous red macule, a mixed macular red and white lesion, or as a red lesion with superimposed white granular spots (speckled leukoplakia). Lesions are most prevalent in the ventral and lateral aspects of the tongue, the retromolar-trigone-soft palate complex, and the floor of the mouth. While often asymptomatic, some patients may complain of discomfort, especially when eating hot or spicy food. The importance of recognizing and evaluating any persistent (over 2 weeks) erythroplakia can not be overemphasized, as evidenced by the fact dysplasia, carcinoma-in-situ, or invasive SCC (Figure 4) is diagnosed microscopically in well over 90% of the lesions characterized clinically as erythroplakia.[34-36]

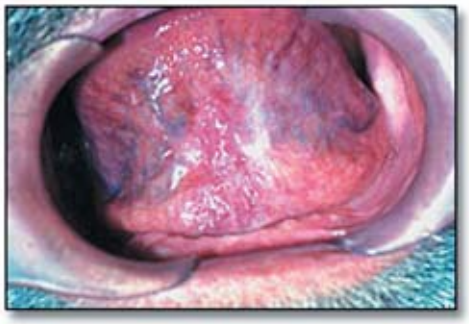


Figure 4. Dysplasia, carcinoma-in-situ, or invasive SCC is diagnosed microscopically in well over 90% of the lesions characterized clinically as erythroplakia.

Leukoplakia

Leukoplakia is a descriptive term for a white lesion of the oral mucosa that cannot be attributed to any other clinically definable lesion.[33] It is most prevalent in the buccal mucosa and mandibular sulcular/alveolar ridge areas, the floor of the mouth, the ventral and lateral aspects of the tongue, and the palate.[37] A recent analysis of 23 studies from across the world reveals a global prevalence of 1.49% to 2.60%, and men are afflicted over three times as often as women.[38] However, recent studies in the United States reported a tendency towards a lower prevalence of oral leukoplakia. The prevalence estimates were 0.37% for homogeneous and 0.06% for non-homogeneous oral leukoplakia. Gingiva (38.8%) and buccal mucosa (30.9%) were the most frequent locations.[69] The rate of malignant transformation of leukoplakia (Figure 5) cannot be predicted accurately, but it is important to acknowledge up to 85% of all precancerous lesions are leukoplakic.[40]

Figure 5. The rate of malignant transformation of leukoplakia cannot be predicted accurately, but it is important to acknowledge that up to 85% of all precancerous lesions are leukoplakic.

Nicotine Stomatitis and Snuff Keratosis

A distinction should be made concerning the use of the term leukoplakia in describing two specific tobacco associated lesions, namely nicotine stomatitis and snuff keratosis. Nicotine stomatitis is a specific red/white lesion attributable to smoking that manifests no increase in malignant transformation and relatively quick resolution after smoking cessation (Figure 6). As the cause is clearly evident, the term leukoplakia does not apply. Likewise, the term leukoplakia should not be applied to the characteristic corrugated white lesion (snuff keratosis, snuff patch, tobacco pouch keratosis) intimately associated with smokeless tobacco placement, since the cause is well

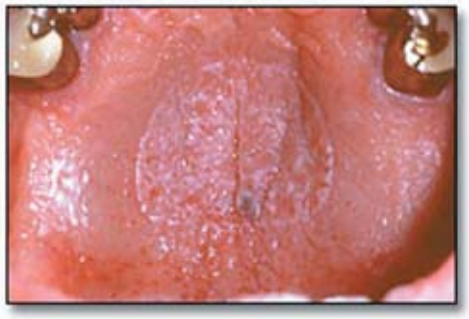


Figure 6. Nicotine stomatitis is a specific red/white lesion attributable to smoking.

established (Figure 7). While there is a tangible risk of dyplasia occurring in snuff keratosis, recent epidemiological data suggests the prevalence of oral epithelial dysplasia in such lesions is generally low[35, 41] While the rate of malignant transformation is low and the process is slow, the relative risk for carcinoma of the buccal/labial mucosa and gingiva among female chronic users is 50 times greater than among non users.[42]

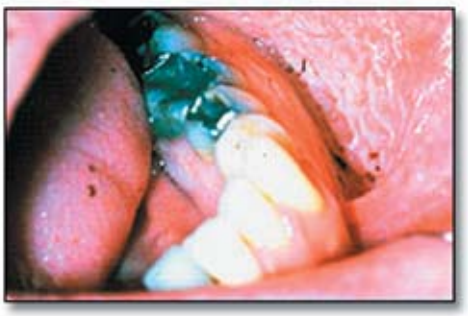


Figure 7. The term leukoplakia should not be applied to the characteristic corrugated white lesion (snuff keratosis, snuff patch, tobacco pouch keratosis) that is intimately associated with smokeless tobacco placement.

Verrucous Leukoplakia

A variation of homogeneous leukoplakia, verrucous leukoplakia, is characterized by surface irregularities (fissuring, corrugation), has a high potential for atypia, and has a high tendency to progress to SCC.[43, 44] The rate of malignant transformation is reported variably to be between 63% and 100%.[45, 46] The lesions appear to favor the mandibular alveoler ridge, gingivae, and buccal mucosa but may involve the palate or the tongue. There is a female predilection (average age of 70 years); although the majority of patients are tobacco smokers, many are not. It is believed verrucous leukoplakia is a precancerous lesion which may progress to verrucous dysplasia, verrucous carcinoma (Figure 8), or invasive SCC. Importantly, verrucous carcinoma does not metastasize, but it may be locally invasive.

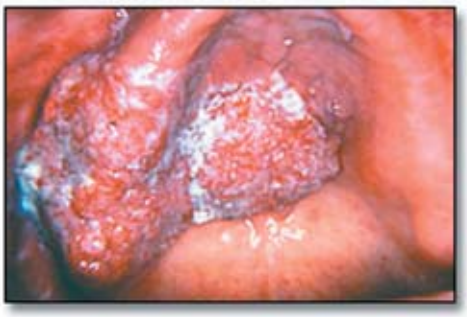


Figure 8. Verrucous leukoplakia is a precancerous lesion which may progress to verrucous dysplasia or verrucous carcinoma.

Lichen Planus

Several studies have reported a significant risk (0.4%-3.7%) for the malignant transformation of oral lichen planus (OLP) to SCC.[47-55] The associative risk appears to be most strongly related to cases of atrophic or erosive OLP (Figure 9).[47, 48, 53, 55-60] There are three likely possibilities to explain the apparent association: (1) OLP transforms into SCC; (2) the impaired epithelium is susceptible to carcinogens, viruses, or chemical irritants; or (3) SCC occurs by coincidence.[61, 62] While those who consider OLP to have an increased risk of malignant transformation focus on the aforementioned first two scenarios, a few critics contend the increased risk is actually a facade caused by an initial misdiagnosis of dysplasia as OLP.[63-66] They contend any histologic evidence of dysplasia noted on biopsy precludes a diagnosis of OLP and further propose the term “lichenoid dysplasia” to account for such findings. However, many others reject such a rigid interpretation as it is limited solely to the histologic aspect of the diagnosis and may ignore or dilute relevant clinical and histologic findings.[53, 67-69] For example, evidence of mild atypia may simply represent inflammation, not an underlying increased risk of malignant transformation. Until this academic debate is settled, the clinician must regularly evaluate, to include biopsy, all cases of OLP to monitor for potential malignant transformation.

Figure 9. The risk of malignant transformation is most strongly related to erosive OLP.

Oral Submucous Fibrosis

Oral submucous fibrosis (OSF) is a pre-cancerous chronic disease of insidious onset characterized by the deposition of fibrous tissues in the submucosal layer of the retromolar area, buccal mucosa, soft palate, uvula, anterior faucial pillars, tongue, labial mucosa, and lips.[70-72] It may extend to involve the pharynx and the esophagus. OSF is seen almost exclusively in adults from southern Asia where its occurrence is strongly associated with the oral habit of betal quid (BQ) chewing.[42, 70, 73, 74] BQ chewing is addicting, and its parasympathomimetic actions induce euphoria, stave off hunger, increase salivation, and induce tremors.[72, 73] The earliest clinical sign of OSF is blanching of the mucosal tissue.[72] This whitish or leukoplakic appearance imparts a marble-like character to the tissues involved, can be quite diffuse, and forms a lace-like network. Requisite to the diagnosis is the presence of palpable fibrous bands.[70, 72] Progressing fibrosis leads to a reduced oral opening; difficulty with mastication, speech, and swallowing; soreness of the throat; and impaired tongue function. The association of OSF and oral cancer is profound with the rate of malignant transformation estimated to be 3% to 19%.[72] In Taiwan 80% of oral cancer deaths are associated with BQ chewing.[73] Finally, the addition of various smokeless tobacco products to the various BQ concoctions appears to further increase the risk of malignant transformation.[42, 75]

Actinic Cheilitis

The short-term effects of exposure to UV light are transient, but the cumulative long-term effects produce irreversible damage (actinic cheilitis), usually to the lower lip of exposed individuals. Actinic cheilitis, a variant of oral leukoplakia, is considered to be the labial counterpart of solar (actinic) keratosis (a precursor of SCC of the skin) (Figure 10).[76] The lips appear dry, mottled, and opalescent with slightly elevated white or gray plaques and that cannot be stripped off. Isolated areas of hyperkeratotic callus may also be evident as well as loss of elasticity and definition of the vermilion border. Other clinical signs include erythematous or hemorrhagic areas, parallel marked folds, and an unobtrusive "chapped lip" appearance. Malignant change is manifested clinically by areas of more diffuse cheilitis and ulcerations of relatively long duration.

Figure 10. Actinic cheilitis, a variant of oral leukoplakia, is considered to be the labial counterpart of solar (actinic) keratosis (a precursor of sqamous cell carcinoma of the skin).

Although degenerative changes have been observed predominantly in men after the age 40, the condition now is increasingly recognized in younger men.[77-79]

Diagnosis

The prediction for 2004 was approximately 563,700 people will die from cancer; of these, 7,230 will die from cancers of the oral cavity and pharynx.[27] Based on these data, North Americans in 2004 will likely die from oral and pharyngeal cancer at a rate of 1.2 per hour. Between 1992 and 1999, at the time of diagnosis, cancers of the oral cavity and pharynx were localized in 34% of the cases, extended to regional lymph nodes in 48% of the case, and presented with distant metastasis in 9% of the cases.[27] The 5-year relative survival rate was 82% when the lesions were localized, 48% when the lesions extended to the regional lymph nodes, and 26% when the lesions presented with distant metastasis. Despite advances in cancer therapies, the overall 5-year survival rate for oral and pharyngeal cancers is still only 57%.[27] Put another way, the percentage of oral cancer localized when diagnosed, is similar to colon cancer, a malignancy that requires endoscopic evaluation.[80] Thus, steps to increase the early diagnosis of this malignancy could drastically reduce mortality, medical costs, pain, and suffering.

The Historical Profile

Medical History

The most important source of preventable morbidity and mortality is tobacco use, which is responsible for one in five deaths in the United States. Historical evidence of cardiovascular diseases (athrosclerotic heart disease); respiratory disorders (chronic bronchitis, emphysema); carcinoma of the lungs, pancreas, and bladder; oral, pharyngeal, laryngeal, or esophageal SCCs; peptic ulcer disease; spontaneous abortions; and giving birth to low birth-weight babies may point to tobacco use.[81-85] This possibility should prompt the clinician to further investigate the patient's family and social histories to elicit information about tobacco use and heighten expectations for increased diagnostic yield associated with the physical examination.

Historical evidence of acquired or therapeutic immunosuppression should alert clinicians to the increased possibility of de novo malignancies.[22, 86-88] SCCs of the skin occur 65 to 250 more frequently in transplant patients compared to the general population.[88] A study of 5,356 post transplant patients in Sweden noted post transplant women had a 126 fold increase risk of developing lip carcinoma and post transplant men had a 38 fold increase for developing lip carcinoma compared to controls.[89] The latency from transplantation to malignancy varies from 3 to 8 years and is inversely related to the patient's age at time of transplant.[88] The incidence varies directly with exposure to ultraviolet radiation; the degree of immunosuppression; and may be related to a variety of oncogenic and nononcogenic HPVs. Compared to SCCs in non transplant patients, these carcinomas tend to grow more rapidly, demonstrate frequent recurrence (13.4%), and a higher rate of metastasis (5% to 8%).[88]

Family History

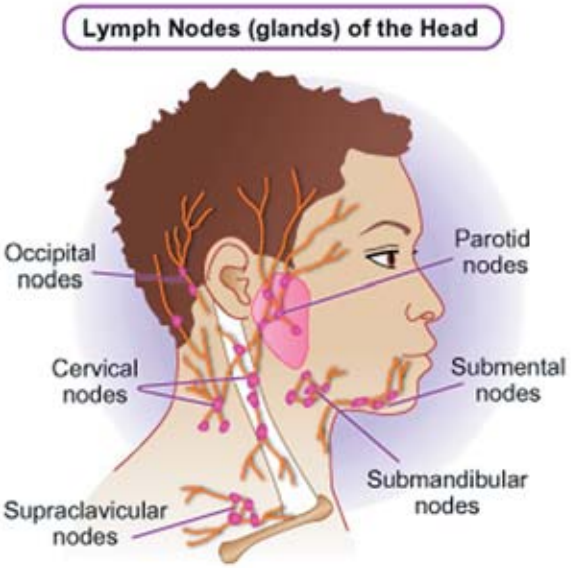
The family history is important in many diseases and, indeed, certain cancers stalk through generation after generation of the same family. In one report having a sibling with oral cancer was associated with an increased risk for developing oral cancer.[90, 91]

Social History

The social history of patients may also provide important clues to facilitate the diagnosis of oral cancer. Extensive use of tobacco and alcohol (particularly among smokers) may produce signs and symptoms whose significance is lost without knowledge of a patient's smoking and drinking habits. The daily use of tobacco should be recorded in numbers of cigarettes (packs), cigars, pipefuls smoked, and the type of smokeless tobacco used. The number of years and increased periodicity a patient used tobacco products and the quality/quantity used has a positive correlation on the incidence of oral cancer. Alcohol consumption should also be recorded in terms of quantity and quality (type) over a specific period of time (per day, per week).

Physical Examination

Physical examination of the patient is of special value in corroborating the findings of the historical profile. It provides an opportunity to identify tobacco-related oral conditions (halitosis, extrinsic discoloration of teeth, gingivitis, necrotizing ulcerative gingivitis, chronic periodontitis, loss of teeth, and precancerous and malignant oral and pharyngeal soft tissue changes). Inspection is the most common examination technique.[92, 93] Note anatomical architecture. Inspect the character of oral mucosal tissues for changes in color, evidence of pigmentations, altered vascularity, and loss of integrity. Palpation provides the examiner with additional information concerning the consistency of tissues, changes in texture, physical characteristics of masses, the presence or absence of tenderness and/or induration, and relation to anatomical structures.



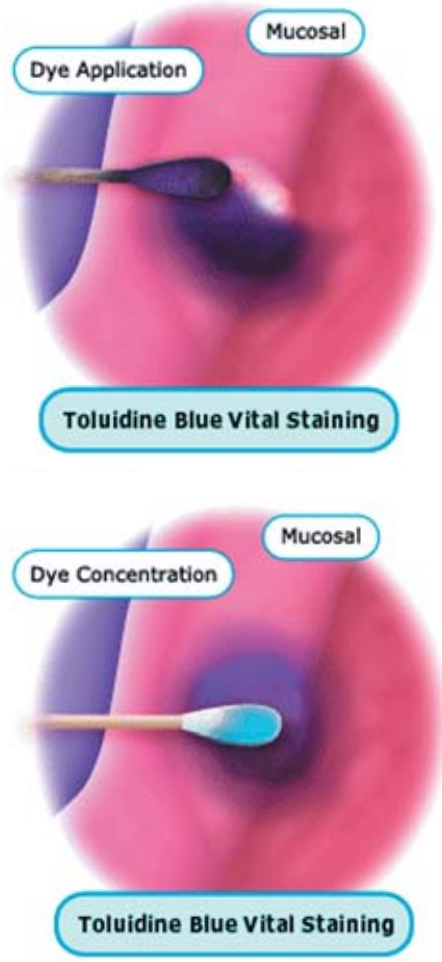
Lymph nodes usually felt and not seen should be evaluated for location, architecture (size, shape, symmetry, and discreetness), consistency, tenderness, mobility, or attachment. Adenopathy of a particular node is an indication of an abnormality that must be explained. Lymphadenopathy associated with intraoral pathosis of various sites involves chiefly the submandibular, submental, and anterior cervical chains. Pathologic changes in the cervical nodes, both inflammatory and neoplastic, may be difficult to distinguish from nonlymphatic tumors or degenerative changes. However, secondary involvement of a lymph node in the neck from a primary malignant lesion (characterized as matted, non tender, usually firm and fixed) of some oral epithelial structure is a most significant finding. Unilateral location indicates metastatic neoplasm and bilateral location indicates primary neoplasm.

Adjunctive Diagnostic Modalities

A knowledge of the more common or high risk sites of involvement of a disease assists in its diagnosis. However, it must be remembered, no diagnostic index or outline can take into consideration the capriciousness of oral cancer and the clinical differentiation between benignity and early stage malignancy is often difficult. Several adjunctive diagnostic modalities have been proposed to aid the clinician to increase the diagnostic yield. Finally, it must be noted no modality, not even the current standard of providing a routine oral cancer screening examination, has been conclusively validated as a cost-effective screening methodology to diagnose oral cancer.[26, 94-96]

Toluidine Blue Vital Staining

Vital staining with the metachromatic dye toluidine blue has been advocated for early detection of oral cancer for many years, especially in high-risk patients, and particularly for those in whom an ordinary visual examination fails to uncover any obvious mucosal changes.[97-102] The dye has an affinity for nuclear material with a high DNA or RNA content, thus, its selective concentration in dysplastic or malignant cells within the epithelilum. Biopsy of stained foci has proven to be highly reliable in detecting malignancy, yet it is not always effective in detecting premalignant lesions. Most investigators advocate its use



as an adjunct to clinical judgment, which may accelerate the decision to perform a biopsy and assist in the selection of the most suspicious site. One commonly expressed concern over the value of TB staining is the fairly high incidence of initial false positives, such as may occur in conditions of trauma or inflammation. However, by employing a protocol to restain any suspicious area in 2 weeks reduces the number of false positives to fewer than 10%.[34] This useful product is commercially available in Europe and several other countries as OraScreenTM (Zila, Inc. Phoenix, Arizona, USA) and is currently undergoing Phase III Trials in the United States.

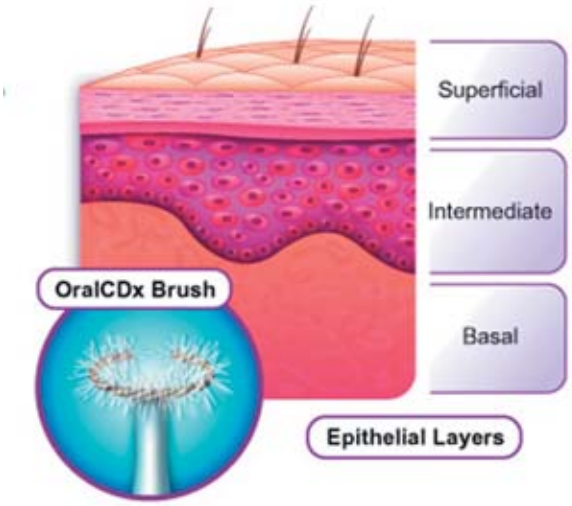
Autofluorescence

Recently, diagnostic methods measuring the specific autofluorescence emitted by cancer tissue upon excitation with laser or xenon light have been developed to aid in the diagnosis of oral SCC.[103, 104] Several studies have confirmed

human oral cancer tissue manifests different autofluoresecence spectra when compared to normal tissue.[103, 105, 106] The high concentrations of protoporphyrin IX present in malignant tissue is believed responsible for this change, which manifests as a red fluorescence.[106-110] Further studies have shown the application of 5-aminolaevulinic acid (ALA) to the mucosa amplifies this measurable shift.[108, 111] Fluorescence photography is being developed and promoted as an adjunctive diagnostic method for SCC, although, ultimately, a biopsy will be necessary.[105-108, 111, 112]

Oral Brush Biopsy

Any innocuous appearing oral epithelial abnormality may be screened for dysplasia or cancer with the oral brush biopsy technique, commercially marketed as the OralCDx kit (OralScanTM Laboratories Inc. Suffern, New York).[113, 114] Each kit contains all the materials and forms necessary to perform and submit the brush biopsy sample. The biopsy brush was specifically designed to obtain a complete trans-epithelial biopsy with minimum discomfort to the patient. No significant bleeding is associated with the procedure and topical or infiltration anesthesia should not be used as it may distort the sample. Proper utilization of this instrument assures an adequate biopsy sample of all three epithelial layers (superficial, intermediate, and basal) of the lesion. All submissions are stained in accordance with a modified Papanicolau method. The stained slides are scanned by the OralCDx computer system specifically designed to detect oral epithelial precancerous and cancerous cells. Images of abnormal cells identified by the computer system are individually displayed on a high-resolution color video monitor for final review by a pathologist.



The brush biopsy technique is specifically indicated to screen those small non-suspicious mucosal lesions that are often trivialized or ignored. The technique is not intended to screen obviously suspicious lesions or to supersede clinical judgment in determining the need to biopsy. Critics argue the technique yields an unacceptably high false positive rate, resulting in unwarranted patient anxiety and biopsy.[115, 116] Others note the possibility of obtaining a false negative report.[117] However, advocates argue the technique has a positive predictive value of 30% to 38% (exceeding the Pap smear and mammography) and leads to earlier cancer diagnosis.[118, 119] While future studies are undertaken to conclusively define the value of the technique, the authors contend, when properly utilized, the brush biopsy serves as a vehicle to increase cancer awareness and ultimately diagnosis the evaluation of the heretofore blissfully ignored small oral lesion.

Chemiluminescence

Neoplastic epithelial cells tend to have an altered nuclear-cytoplasmic ratio. Dehydration with acetic acid highlights this higher nuclear density and imparts an “acetowhite” appearance to tissues.[120] This phenomenon can be further amplified by replacing conventional lighting with diffuse blue-white chemiluminescent illumination.[121-123] The normal epithelium takes on a blue hue, while the “acetowhite” lesions appear distinctly white. This strategy has been shown to increase the detection of biopsy proven epithelial dysplasia and malignancy of the cervix and lower genital tract when compared with naked eye or magnified visualization under incandescent or halogen projected lighting.[121-124]

A chemiluminescent illumination system to examine the oral mucosa is available commercially (ViziLiteTM, Zila Inc. Phoenix, Arizona, USA). The technique is painless, easy to learn, and may ultimately identify suspicious lesions missed during visual inspection under incandescent overhead and halogen dental illumination. Data from a pilot study provides

strong evidence to support the hypothesis the oral epithelium exhibits features similar to those of the cervical epithelium following an acetic acid wash and visual inspection under chemiluminescent illumination.[125] Epithelium with an altered nuclear-cytoplasmic ration does reflect the diffuse, low-level, blue-white chemiluminescet light and the lesions become clinically discernible and appear "acetowhite." These bright white lesions are sharply demarcated from the adjacent, normal epithelium, which takes on a blue hue. However, several benign oral lesions (leukoedema, frictional irritation, lichenoid mucositis) readily recognized because of their clinical appearance, bilateral nature, and anatomic distribution may be misinterpreted as positive because epithelium with hyperketatinization, hyperparakeratinization, and/or chronic inflammatory infiltrate reflects the diffuse, low-level, blue-white chemiluminescent light more strongly than normal tissue and appear amplified. Large-scale studies are required to further refine issues related to the selectivity and specificity of the technology in correlation with the clinical, cytological, and histological features of oral epithelial lesions.

Histopathology

There are striking similarities among the many lesions affecting oral tissues. It is essential in the differential diagnostic process to consider all possibilities before making a definitive diagnosis. In some instances a history of the pathogenesis aided by the clinical or radiographic characteristics and laboratory profiling may confirm the clinical impression. However, at other times, a biopsy may be required to arrive at a specific diagnosis and biopsy remains the gold standard by which oral cancer is diagnosed. A biopsy may be either excisional or incisional. An excisional biopsy is the technique of choice when a lesion is relatively small. The lesion is excised in its entirety. An incisional biopsy is indicated when a lesion is large. A pie-shaped wedge is removed to include both normal and abnormal tissue. In some instances several specimens may have to be taken for adequate microscopic evaluation.

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

Evaluation of the location and extent of squamous cell tumors can be done with both CT and MRI. CT has long been regarded as the imaging modality of choice for assessing the size, location, and spread (both in soft tissue and regional lymph nodes) of the primary tumor.[126] The newer MRI technology offers potential advantages in terms of superior soft tissue contrast, multiplanar imaging capability, lack of ionizing radiation, and freedom from metallic artifacts from dental restorations.[127-130] In the mandible CT outperforms MRI in determining cortical involvement, but MRI is more reliable in evaluation extension of the tumor into marrow.[131-133] Ultimately, none of the imaging techniques are accurate enough by themselves, and a combination of clinical and multiple imaging techniques offer the best results in determining the degree of osseous involvement.[134]

Principles Of Medical Management

Based on the size of the primary neoplasm (T), the extent of lymph node involvement (N), and the presence of distant metastasis (M), head and neck cancers are staged (Table 1).[135] Staging is a useful tool for treatment planning, prognostication, and comparison of treatment outcomes. Medical management is coordinated by multidisciplinary teams whose members deliver all therapeutic anti tumor modalities and provide appropriate adjunctive services such as dental care and nutritional, psychological, and social support.[136] Team members may include a head and neck and/or plastic surgeon, a general and/or oral and maxillofacial pathologist, a radiation and a medical oncologist, oral healthcare providers, a nutritionist, a nurse specialist, a speech pathologist, and a tobacco cessation counselor.[35] Typically, head and neck cancer is treated by one or a combination of the three principal therapeutic modalities: surgery, radiotherapy, and chemotherapy.[137-141] The use of one treatment over another depends on the size, location, and stage of the primary tumor, the patient's ability to tolerate treatment, and the patient's desires. Surgical excision is the preferred modality for most well-defined and accessible solid tumors; however, it has its limitations for inaccessible or more advanced tumors demonstrating lymph node involvement and/or metastasis.[31, 35, 75, 142-144] For such cases, radiotherapy may be either an effective alternative to surgery or a valuable adjunct to surgery and/or chemotherapy in the locoregional treatment of

Table 1. Head and neck cancer staging.[135]

Stage	Tumor size (T)	Regional Lymph nodes (N)	Distant metastasis (M)
I T1, N0, M0	T1: ≤ 2cm	No lymph nodes involvement (N0)	No distant metastasis (M0)
II T2, N0, M0	T2: 2 - 4 cm	No lymph nodes involvement (N0)	No distant metastasis (M0)
III T1, N1, M0 T2, N1, M0 T3, N1, M0 T3, N0, M0	T1, T2, T3 T3: > 4cm	No lymph nodes involvement (N0) Cancer may spread to single ipsilateral lymph node not more than 3 cm in greatest dimension (N1)	No distant metastasis (M0)
IV T4, N0, M0 T4, N1, M0 Any T, N2, M0 Any T, N3, M0 Any T, Any N, M1	T1, T2, T3, T4 T4: Tumor invades adjacent structures	(N0) (N1) Cancer may spread to single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or to multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension (N2) Cancer may spread to a lymph node more than 6 cm in greatest dimension (N3)	Distant metastasis may or may not present (M0, M1)

malignant head and neck tumors.[136, 142, 143, 145-151] While the benefit of neoadjuvant (induction) chemotherapy has been recently scrutinized, several studies have shown concomitant chemoradiotherapy improves both locoregional control and survival.[31, 136-139, 141, 147, 152, 153]

Prognosis may be influenced by patient-related factors (age, sex, performance status, clinical symptoms, comorbidity), tumor-related factors (histologic type and grade, vascular and perineural invasion, receptors, genetic abnormalities, ploidy, proliferation), and treatment-related factors (surgical technique, dose and intensity of radiation, chemotherapy). Among these different putative factors there may exist a multitude of interactions of different strength. Dramatic advances in our understanding of the molecular mechanisms involved in cancer biology may not only improve our ability to diagnose and treat cancer, but improve prevention and may have prognostic value.[36, 154-165] Putative markers under study include loss of heterozygosity (LOH), DNA ploidy, numerous tumor suppressor genes (p53, retinoblastoma gene, others), and proto-oncogenes (epidermal growth factor receptor gene, members of the ras gene family, c-Myc gene, cyclin D1 gene, and others). It has been shown recently, in spite of surgical resection, aneuploid oral leukoplakia was strongly associated with the development of aggressive carcinoma and death from oral cancer.[162]

Principles of Dental Management

The care of patients with head and neck cancer undergoing treatment or who have completed treatment is a multidisciplinary effort. Oral healthcare providers can expect to be called upon to care for patients with head and neck cancer. Early, active participation in developing preventive and therapeutic strategies, in implementing the plan, and in the education and rehabilitation of the patient is paramount in addressing quality of life issues. To provide timely and competent care, oral healthcare providers must understand the disease, its treatment, and the impact the disease and/or its treatment may have on these patients. Oral healthcare providers should develop and implement preventive and therapeutic strategies with the same ethical, moral, and professional standards of care as may be appropriate in the management of other patients. A comprehensive discussion of the principles of dental management of patients undergoing head and neck radiotherapy and/or chemotherapy has been recently presented.[166, 167]

Summary

Because the essence of malignancy escapes full understanding, prevention must be equated with early detection. The general dentist is clearly responsible for early detection, in the head and neck area. This is especially true for oral soft tissue lesions. Appropriate diagnostic procedures must be implemented as a matter of course in the evaluation of any lesion not responding to usual therapy in 7 to 14 days and when a malignancy is suspected. To safeguard and advance the welfare of the patient, whenever the diagnosis is in doubt, the clinician has the obligation to initiate consultation with or referral to a respected peer or specialist with special skills, knowledge, and experience.

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